

## Sultamo-Steroid Analogues, Part VII: Synthesis of Epi-Androsterone Derivatives with Potential Activity

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The reaction of epi-androsterone with cyanoacetyl hydrazine (2) gave the hydrazone derivative 3. The reactivity of 3 towards chemical reagents was studied to give pyridine, thiazole and thiophene derivatives.

**Key words:** Epi-androsterone, Malononitrile, Pyridine

### INTRODUCTION

The synthesis of steroidal compounds having heterocyclic ring system proved to be an easy, facile and sole approach for the synthesis of hitherto unreported derivatives of polyfunctionally substituted pyridines, thiophenes, thiazoles and pyrazoles (Siddiqui *et al.*, 1993; Irismetov *et al.*, 1994; Hajos, 1993; Rapole *et al.*, 1996; Banerjee *et al.*, 1992). The importance of such derivatives is due to their diverse biological and physiological potentialities as they are known to exhibit anti-epileptic (Helferich, 1960; Helferich and Doss 1970 and 1971), antiprotozoal (Mallick *et al.*, 1971), bactericidal (Dhal *et al.*, 1975) antitumor (Also *et al.*, 1997) and hypoglycemic activities (William *et al.*, 1970). In this article, we report the use of 3 $\beta$ -hydroxy-5 $\alpha$ -androstan-17-one (epi-androsterone) as the key starting material for such synthetic routes.

### RESULTS AND DISCUSSION

The reaction of 3 $\beta$ -hydroxy-5 $\alpha$ -androstan-17-one (epi-androsterone, 1) with cyanoacetyl hydrazine (2) in acetic acid solution gave the hydrazone derivative 3. The structure of 3 was established on the basis of IR spectra, which revealed the presence of NH group stretching at 3420-3380  $\text{cm}^{-1}$  and CN group stretching at 2228  $\text{cm}^{-1}$ . The  $^1\text{H}$  NMR spectra revealed the presence of a singlet peak at  $\delta$  3.15 ppm for  $\text{CH}_2$  group and  $\text{D}_2\text{O}$ -exchangeable singlet signal at  $\delta$  10.20 ppm for NH group.

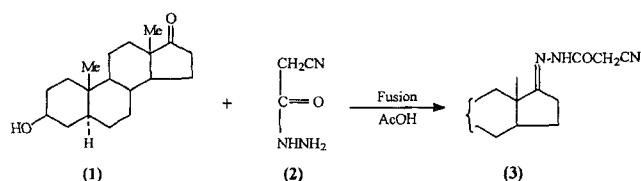


Fig. 1. Preparation of Compound 3

The reaction of 3 with benzenediazonium chloride gave the phenylhydrazone derivative 4, the structure of 4 was established on the basis of IR and  $^1\text{H}$  NMR spectra, which revealed the presence of the phenyl protons at  $\delta$  7.32-7.49 ppm.

The reaction of 3 with malononitrile in dimethylformamide containing a catalytic amount of triethylamine gave the pyridine derivative 5. The structure of 5 was established on the basis of IR spectra, which showed the presence of two amino groups at 3440, 3420  $\text{cm}^{-1}$  and one CN group at 2220  $\text{cm}^{-1}$ .

The reaction of 3 with freshly prepared benzoyl-

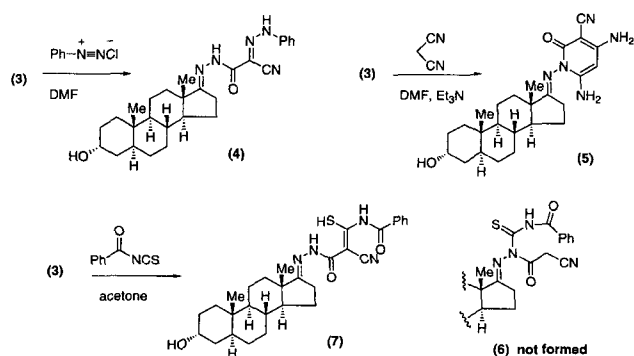


Fig. 2. Preparation of compound 4,5,7

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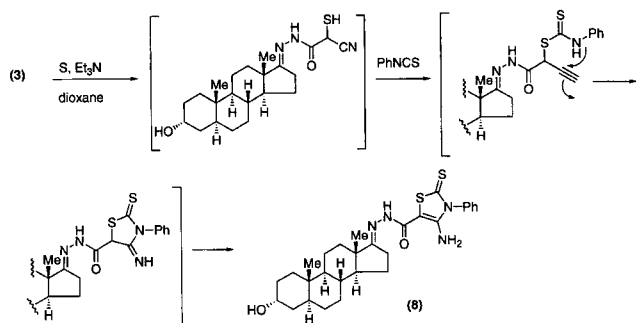


Fig. 3. Preparation of compound 8

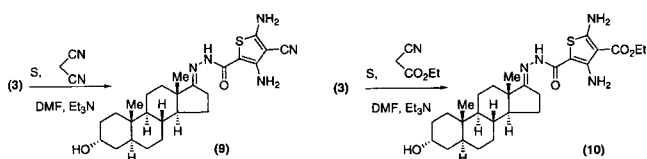


Fig. 4. Preparation of compound 9,10

isothiocyanate afforded a single product with molecular formula  $C_{30}H_{38}N_4SO_3$ . Two possible isomeric structures were proposed for such formula **6** and **7**. Structure **7** was established for the reaction product on the basis of IR spectrum of the product which revealed a  $C=O$  group at  $1695\text{ cm}^{-1}$ . The  $^1\text{H}$  NMR spectrum revealed the presence of two  $\text{D}_2\text{O}$ -exchangeable signals at  $\delta$  8.23 ppm and  $\delta$  8.34 ppm for two NH groups and a multiplet peak at  $\delta$  7.32-7.58 ppm for phenyl group.

The reaction of **3** with elemental sulphur and phenylisothiocyanate in 1,4-dioxane in the presence of a catalytic amount of triethylamine afforded the thiazole derivative **8**. On the other hand, the reaction of **3** with malononitrile or ethyl cyanoacetate in the presence of elemental sulphur gave the thiophene derivatives **9** and **10** respectively. The structures of compounds **8**, **9** and **10** were established on the basis of analytical and spectral data (cf. Tables I, II).

The reactivity of 3 $\beta$ -hydroxy-5 $\alpha$ -androstane-17-one (**1**) with other hydrazines and hydrazides was studied. Thus **1** was reacted with phenylhydrazine to form the corresponding hydrazine derivative **11**. On the other hand from the reaction of **1** with benzoyl-hydrazine, the benzoyl-hydrazine derivative **12** was formed. Similarly, the reaction of **1** with acetylhydrazine gave the acetyl-hydrazine derivative **13**. Compound **11** readily underwent cyclization when heated in concentrated sulphuric acid/acetic acid mixture (1:10) to give 3 $\beta$ -hydroxy-5 $\alpha$ -androstane [17,16-*b*]indole derivative **14**. Structures of compound **11**, **12**, **13** and **14** were established on the basis of analytical spectral data as shown in Table I and Table II.

The reaction of **10** with 4-phenyl-3-thiosemicarbazides **15** and **16** afforded the corresponding 17-(4'-phenyl-3'-

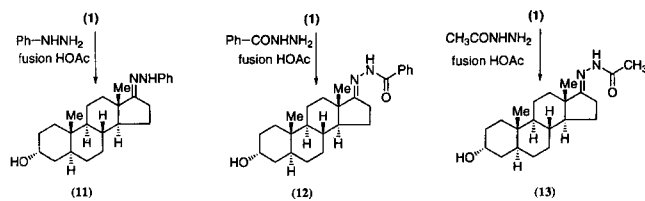


Fig. 5. Preparation of compound 11,12,13

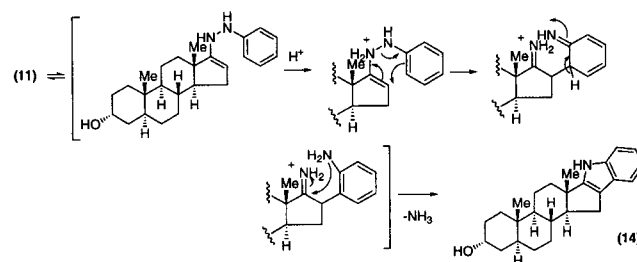


Fig. 6. Preparation of compound 14

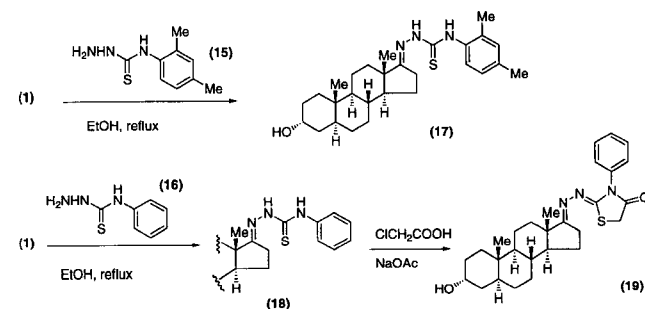


Fig. 7. Preparation of compound 17,18,19

thiosemicarbazone derivatives **17** and **18**, respectively. Compound **18** on treatment with monochloroacetic acid in the thiazolidinone derivative **19**. The structure of compound **17**, **18** and **19** were established based on analytical and spectral data as shown in Table I and Table II.

The reaction of **1** with malononitrile afforded the condensed product **20**. Structure of **20** was confirmed on the basis of IR spectrum which revealed the presence of two CN group at  $2225$  and  $2220\text{ cm}^{-1}$  (cf. Table II).

The reaction of **1** with hydroxylamine hydrochloride in ethanol afforded the oxime derivative **21**, which readily underwent cyclization through the Beckmann rear-

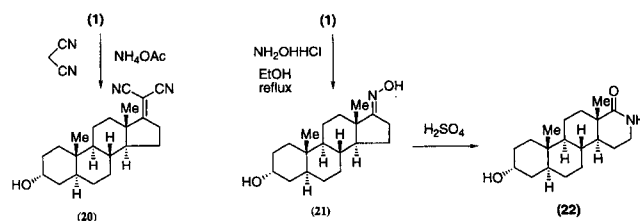


Fig. 8. Preparation of compound 20,21,22

ring expansion when heated in concentrated sulphuric acid using a boiling water bath to give the pyridin-2-one derivative **22**, as similar ring expansion reactions reported in several literatures (Shafiullah *et al.*, 1986; Shafiullah *et al.*, 1990; Jindal *et al.*, 1996).

### Scanning for anti-tumor effects

Some of the compounds in this work showed anti-tumor effects against Ehrlich ascites tumors as demonstrated by the cylinder agar plate method (Hayahi *et al.*, 1962). The data of this work will be published through next article.

## MATERIALS AND METHODS

Melting points were uncorrected. IR spectra (KBr disks) were recorded on a Pye Unicam SP-100 spectrometer. <sup>1</sup>H NMR spectra (DMSO-d<sub>6</sub> as solvent) were obtained on a Varian A.90 spectrometer using SiMe<sub>4</sub> as an internal standard, chemical shifts were expressed as δ (ppm) values. Analytical data were obtained from the Micro-analytical data unit at Cairo University and National Research Centre.

### 3β-Hydroxy-5α-androstan-17-cyanoacetyl hydrazone (3)

To a suspension of **1** (2.9 g, 0.01 mol) in acetic acid (0.5 ml) cyanoacetyl hydrazine **2** (0.99 g, 0.01 mol) [prepared by the addition of hydrazine hydrate (5 ml, 0.1 mol) to ethyl cyanoacetate (11.3 g, 0.1 mol) with stirring

at room temperature] was added. The reaction mixture was heated in an oil bath at 120°C for 10 min and the solid product formed upon cooling was triturated with ethanol and collected by filtration and crystallized from the appropriate solvent (Table I) to afford **3** (2.89 g, 78%).

### 3β-Hydroxy-5α-androstan-17-(α-phenylhydrazonocyanacetyl hydrazone (4)

To a cold solution of **3** (3.7 g, 0.01 mol) at 0°C in dimethylformamide (20 ml) containing sodium acetate (2.0 g) a solution of benzenediazonium chloride [prepared by the addition of sodium nitrite solution (0.01 mol) to a cold suspension of aniline (0.1 mol) containing the appropriate amount of hydrochloric acid with stirring] was added with stirring. The solid product, formed upon dilution with water was collected by filtration and crystallized from the appropriate solvent (Table I) to afford **4** (3.70 g, 78%).

### 3β-Hydroxy-17-(4,6-diamino-3-cyano-1<sup>H</sup>-2-oxopyridine-1-ylimino)-5α-androstane (5)

To a solution of **3** (1.85 g, 0.005 mol) in dimethylformamide (20 ml) containing triethylamine (0.5 ml), malononitrile (0.33 ml, 0.005 mol) was added. The reaction mixture was heated under reflux for 4 h then left to cool and the solid product formed was collected by filtration and crystallized from the appropriate solvent (Table I) to afford **5** (1.42 g, 65%).

**Table I.** Melting points, Yields and Elemental Analysis for Compounds 3-22

Compd <sup>a</sup>	m.p.	Elemental Analysis Found (Calcd.)			
	°C	C	H	N	S
<b>3</b>	239-42	71.0 (71.15)	8.6 (8.89)	11.0 (11.32)	
<b>4<sup>b</sup></b>	118-20	70.5 (70.73)	7.5 (7.78)	14.2 (14.73)	
<b>5<sup>c,d</sup></b>	268-71	68.5 (68.64)	7.7 (8.00)	15.7 (16.01)	
<b>7</b>	218-21	67.1 (67.41)	7.3 (7.11)	10.0 (10.45)	5.8 (5.99)
<b>8</b>	118-21	64.9 (64.68)	6.8 (7.06)	10.4 (10.51)	12.1 (11.89)
<b>9<sup>b</sup></b>	261-63	63.7 (63.96)	7.2 (7.46)	14.8 (14.92)	6.6 (6.82)
<b>10</b>	> 300	62.6 (62.79)	7.5 (7.75)	10.4 (10.85)	6.0 (6.2)
<b>11</b>	147-49	78.7 (78.94)	9.5 (9.74)	7.6 (7.63)	
<b>12<sup>b,c</sup></b>	238-40	76.5 (76.74)	8.7 (8.82)	6.6 (6.86)	
<b>13</b>	236-38	72.5 (72.83)	9.4 (9.82)	7.9 (8.09)	
<b>14<sup>d</sup></b>	189-91	82.4 (82.64)	8.9 (9.09)	3.6 (3.85)	
<b>17</b>	253-55	71.7 (71.94)	8.4 (8.78)	6.7 (6.85)	
<b>18</b>	228-30	71.3 (71.07)	8.2 (8.42)	9.1 (9.56)	7.0 (7.29)
<b>19<sup>e</sup></b>	186-88	70.0 (70.14)	7.4 (7.72)	8.4 (8.76)	6.2 (6.68)
<b>20<sup>b,d</sup></b>	218-20	77.8 (78.16)	8.7 (8.87)	8.0 (8.28)	
<b>21</b>	148-51	74.5 (74.75)	10.0 (10.26)	4.4 (4.59)	
<b>22<sup>b,e</sup></b>	> 300	74.6 (74.75)	10.0 (10.16)	4.3 (4.59)	

<sup>a</sup>In case of no other notes, all compounds are colorless and were crystallized from EtOH <sup>b</sup>Yellow <sup>c</sup>From MeOH <sup>d</sup>From EtOH-DMF <sup>e</sup>From DME.

**3 $\beta$ -Hydroxy-5 $\alpha$ -androstane-17-( $\alpha$ -benzoylamino- $\alpha$ -mercaptomethino-ylidino)cynoacetyl hydrazone (7)**

To a freshly prepared benzoylthiocyanate [prepared by the addition of benzoyl chloride (1.35 g, 0.01 mol) to a solution of potassium thiocyanate (0.97 g, 0.01 mol) in acetone (20 ml) and the reaction mixture was heated under reflux for 20 min] a solution of **3** (3.7 g, 0.01 mol) in acetone (30 ml) was added. The reaction mixture was heated under reflux for 3 h. The solid product formed upon dilution with water was collected by filtration and crystallized from the appropriate solvent (Table I) to afford **7** (4.16 g, 78%).

**3 $\beta$ -Hydroxy-17-(4-amino-3-phenyl-2-thioxothiazole-5-carbonylhydra-zono)-5 $\alpha$ -androstane (8)**

To a solution of **3** (1.85 g, 0.005 mol) in 1,4-dioxane (30 ml) containing triethylamine (0.5 ml), elemental sulphur (0.16 g, 0.005 mol) was added followed by phenyl isothiocyanate (0.67 ml, 0.005 mol). The reaction mixture was heated under reflux for 5 h then left to cool and the solid product formed was collected by filtration and crystallized from the appropriate solvent (Table I) to afford **8** (1.80 g, 67%).

**3 $\beta$ -Hydroxy-17-(3,5-diamino-4-cyanothiophene-2-carbonylhydra-zono)-5 $\alpha$ -androstane (9)**

To a solution of **3** (1.85 g, 0.005 mol) in dimethylformamide (20 ml) containing triethylamine (0.5 ml), elemental sulphur (0.16 g, 0.005 mol) was added followed by malononitrile (0.33 ml, 0.005 mol). The reaction mixture was heated under reflux for 5 h then left to cool. The formed solid product was collected by filtration and crystallized from the appropriate solvent (Table I) to afford **9** (1.47 g, 63%).

**3 $\beta$ -Hydroxy-17-(3,5-diamino-4-ethoxycarbonylthiophene-2-carbonyl-hydra-zono)-5 $\alpha$ -androstane (10)**

To a solution of **3** (1.85 g, 0.005 mol) in dimethylformamide (20 ml) containing triethylamine (0.5 ml), elemental sulphur (0.16 g, 0.005 mol) was added followed by ethyl cyanoacetate (0.56 ml, 0.005 mol). The reaction mixture was heated under reflux for 5 h then left to cool. The formed solid product was collected by filtration and crystallized from the appropriate solvent (Table I) to afford **10** (1.72 g, 67%).

**3 $\beta$ -Hydroxy-5 $\alpha$ -androstane-17-phenylhydrazone (11)**

To a suspension of **1** (2.9 g, 0.01 mol) in acetic acid (0.5 ml), phenylhydrazine (1 ml, 0.01 mol) was added. The reaction mixture was heated in an oil bath at 120°C for 10 min. The reaction product formed upon cooling was triturated with ethanol, collected by filtration and crystallized from the appropriate solvent (Table I) to afford **11** (2.66 g, 70%).

**3 $\beta$ -Hydroxy-5 $\alpha$ -androstane-17-benzoylhydrazone (12)**

To a suspension of **1** (2.9 g, 0.01 mol) in acetic acid (0.5 ml), benzoylhydrazine (1.36 ml, 0.01 mol) [prepared by the addition of excess of hydrazine hydrate (12 ml) to methyl benzoate (13.6 g, 0.1 mol) with stirring] was added. The reaction mixture was heated in an oil bath at 120°C for 15 min. The solid product formed upon cooling was triturated with ethanol, collected by filtration and crystallized from the appropriate solvent (Table I) to afford **12** (3.06 g, 75%).

**3 $\beta$ -Hydroxy-5 $\alpha$ -androstane-17-acetylhydrazone (13)**

To a suspension of **1** (2.9 g, 0.01 mol) in acetic acid (0.5 ml), acetylhydrazine (0.74 ml, 0.01 mol) [prepared by the addition of excess of hydrazine hydrate (8 ml) to ethylacetate (8.8 ml, 0.1 mol) and heating under reflux for 2 h] was added. The reaction mixture was heated in an oil bath at 120°C for 10 min. The solid product formed upon cooling was triturated with ethanol, collected by filtration and crystallized from the appropriate solvent (Table I) to afford **13** (2.83 g, 82%).

**3 $\beta$ -Hydroxy-5 $\alpha$ -androstane[17,16-*b*]indol derivative (14)**

To a solution of **11** (3.8 g, 0.01 mol) in acetic acid (30 ml), concentrated sulphuric acid (3 ml) was added. The reaction mixture was heated under reflux for 3 h. The solid product formed upon dilution with water was collected by filtration and crystallized from the appropriate solvent (Table I) to afford **14** (2.83 g, 78%).

**3 $\beta$ -Hydroxy-5 $\alpha$ -androstane-17-(2',4'-dimethyl-4''-phenyl-3''-thiosemi-carbazone) (17)**

To a solution of **1** (2.9 g, 0.01 mol) in ethanol (30 ml), 2', 4'-di-methyl-4-phenyl-3-thiosemicarbazide **15** (1.95 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 5 h then left to cool. The solid product formed was collected by filtration and crystallized from the appropriate solvent (Table I) to afford **17** (3.17 g, 68%).

**3 $\beta$ -Hydroxy-5 $\alpha$ -androstane-17-(4-phenyl-3-thiosemicarbazone) (18)**

To a solution of **1** (2.9 g, 0.01 mol) in ethanol (30 ml), 4-phenyl-3-thiosemicarbazide **16** (1.67 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 4 h then left to cool. The solid product formed was collected by filtration and crystallized from the appropriate solvent (Table I) to afford **18** (2.89 g, 68%).

**3 $\beta$ -Hydroxy-20-hydrazino (1,3-thiazolin-3-phenyl-2-yliden-4-one)-5 $\alpha$ -androstane (19)**

To a solution of **18** (2.19 g, 0.005 mol) in acetic acid (40 ml), monochloroacetic acid (0.47 ml, 0.005 mol) and

**Table II.** IR and <sup>1</sup>H NMR Spectral Data for Compounds 3-22

Compd.	IR (cm <sup>-1</sup> )	<sup>1</sup> H NMR δ (ppm)
3	3300-3550 (OH, NH), 2980, 2880 (CH <sub>3</sub> , CH <sub>2</sub> ), 2228 (CN), 1701 (C=O), 1640 (C=N).	10.20 (s, 1H, NH), 10.63 (s, 1H, OH), 3.15 (s, 2H, CH <sub>2</sub> ).
4	3330-3580 (OH, NH), 3050 (CH-aromatic), 2970, 2890 (CH <sub>3</sub> , CH <sub>2</sub> ), 2225 (CN), 1720 (C=O), 1660 (C=N).	7.35-7.49 (m, 5H, C <sub>6</sub> H <sub>5</sub> ), 10.00, 10.45 (2s, 2H, 2NH), 12.56 (s, 1H, OH).
5	3320-3580 (OH, 2NH <sub>2</sub> ), 3060 (pyridine-CH), 2985, 2890 (CH <sub>3</sub> , CH <sub>2</sub> ), 2220 (CN), 1700 (C=O), 1660 (C=N).	3.43, 3.62 (2s, 4H, 2NH <sub>2</sub> ), 7.53 (s, 1H, pyridine H-3), 10.21 (s, 1H, OH).
7	3380-3560 (OH, 2NH), 3060 (CH-aromatic), 2975, 2885 (CH <sub>3</sub> , CH <sub>2</sub> ), 2225 (CN), 1695 (C=O), 1660 (C=N), 1635 (C=C).	4.58 (s, 1H, SH), 7.32-7.58 (m, 5H, C <sub>6</sub> H <sub>5</sub> ), 8.23, 8.34 (2s, 2H, 2NH), 10.21 (s, 1H, OH).
8	3490-3380 (OH, NH, NH <sub>2</sub> ), 3050 (CH-aromatic), 2970, 2880 (CH <sub>3</sub> , CH <sub>2</sub> ), 1690 (C=O), 1660 (C=N), 1630 (C=C), 1200-1190 (C=S).	Insoluble in usual <sup>1</sup> H NMR solvents.
9	3650-3420 (OH, 2NH <sub>2</sub> , NH), 2980, 2870 (CH <sub>3</sub> , CH <sub>2</sub> ), 2220 (CN), 1680 (C=O), 1635 (C=C).	3.49, 3.56 (2s, 4H, 2NH <sub>2</sub> ), 8.21 (s, 1H, NH), 10.31 (s, 1H, OH).
10	3340-3460 (OH, NH, NH <sub>2</sub> ), 2980, 2885 (CH <sub>3</sub> , CH <sub>2</sub> ), 1760, 1700 (2C=O), 1650 (C=N), 1635 (C=C).	1.31 (t, 3H, CH <sub>3</sub> ), 2.23, 2.18 (2s, 4H, 2NH <sub>2</sub> ), 4.41 (q, 2H, CH <sub>2</sub> ), 4.5 (s, 1H, NH), 10.41 (s, 1H, OH).
11	3550-3420 (OH, NH), 3065 (CH-aromatic), 2950, 2870 (CH <sub>3</sub> , CH <sub>2</sub> ), 1650 (C=N), 1630 (C=C).	4.23 (s, 1H, NH), 7.50-7.78 (m, 5H, C <sub>6</sub> H <sub>5</sub> ), 10.68 (s, 1H, OH).
12	3490-3420 (OH, NH), 3060 (CH-aromatic), 2985, 2860 (CH <sub>3</sub> , CH <sub>2</sub> ), 1680 (C=O), 1645 (C=N), 1632 (C=C).	3.68 (s, 1H, NH), 7.48-7.70 (m, 5H, C <sub>6</sub> H <sub>5</sub> ), 10.23 (s, 1H, OH).
13	3560-3280 (OH, NH), 2975, 2860 (CH <sub>3</sub> , CH <sub>2</sub> ), 1680 (C=O), 1660 (C=N), 1630 (C=C).	3.68 (s, 1H, NH), 9.55 (s, 1H, NH), 10.36 (s, 1H, OH).
14	3580-3290 (OH, NH), 3050 (CH-aromatic), 2975, 2900 (CH <sub>3</sub> , CH <sub>2</sub> ), 1635 (C=C).	2.68 (s, 1H, NH), 7.32-7.57 (m, 5H, C <sub>6</sub> H <sub>5</sub> ), 10.38 (s, 1H, OH).
17	3520-3280 (OH, NH), 3060 (CH-aromatic), 2970, 2920 (CH <sub>3</sub> , CH <sub>2</sub> ), 1660 (C=N), 1630 (C=C), 1200-1195 (C=S).	2.20, 2.22 (2s, 6H, 2CH <sub>3</sub> ), 7.30-7.35 (m, 3H, C <sub>6</sub> H <sub>5</sub> ), 10.50, 10.68 (2s, 2H, 2NH), 10.88 (s, 1H, OH).
18	3620-3480 (OH, NH), 3060 (CH-aromatic), 2970, 2890 (CH <sub>3</sub> , CH <sub>2</sub> ), 1660 (C=N), 1630 (C=C), 1200-1190 (C=S).	7.23-7.51 (m, 5H, C <sub>6</sub> H <sub>5</sub> ), 9.50-9.53 (2s, 2H, 2NH), 10.42 (s, 1H, OH).
19	3620-3420 (OH), 3050 (CH-aromatic), 2980, 2895 (CH <sub>3</sub> , CH <sub>2</sub> ), 1690 (C=O), 1665, 1650 (2C=N), 1630 (C=C).	Insoluble in usual <sup>1</sup> H NMR solvents.
20	3580-3420 (OH), 2970, 2895 (CH <sub>3</sub> , CH <sub>2</sub> ), 2225, 2220 (2CN), 1635 (C=C).	Insoluble in usual <sup>1</sup> H NMR solvents.
21	3520-3280 (2OH), 2975, 2920 (CH <sub>3</sub> , CH <sub>2</sub> ), 1660 (C=N).	7.27 (s, 1H, NH), 10.26 (s, 1H, OH).
22	3570-3360 (OH, NH), 1710 (C=O), 2980, 2910 (CH <sub>3</sub> , CH <sub>2</sub> ).	8.21 (s, 1H, NH), 10.23 (s, 1H, OH).

anhydrous sodium acetate (0.5 g) were added and the reaction mixture was heated under reflux for 6 h. The solid product formed upon dilution with water was collected by filtration and crystallized from the appropriate solvent (Table I) to afford **19** (1.67 g, 70%).

### 3β-Hydroxy-5α-androstan-17-dicyanomethane (20)

To a mixture of **1** (2.9 g, 0.01 mol) and ammonium acetate (1.5 g), malononitrile (0.66 g, 0.01 mol) was added. The reaction mixture was heated in an oil bath at 120°C for 15 min. The solid product formed upon cooling was triturated with ethanol, collected by filtration and crystallized from the appropriate solvent (Table I) to afford **20** (2.63 g, 78%).

### 3β-Hydroxy-5α-androstan-17-oxime (21)

To a solution of **1** (2.9 g, 0.01 mol) in ethanol (30 ml) containing anhydrous sodium acetate (1.5 g) a solution

of hydroxylamine hydrochloride (0.7 g, 0.01 mol) in water (5 ml) was added. The reaction mixture was stirred at 25°C for 30 min then poured into water. The solid product formed was collected by filtration and crystallized from the appropriate solvent (Table I) to afford **21** (2.59 g, 85%).

### Pyridine-2-one derivative (22)

Concentrated sulphuric acid (5 ml) was added to the oxime **21** (3 g, 0.01 mol) and the reaction mixture was heated in a boiling water bath for 1 h. The solid product formed upon dilution with water was collected by filtration and crystallized from the appropriate solvent (Table I) to afford **22** (2.50 g, 82%).

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